

Appl. Serial No.: 09/646,924
Attorney Docket No.: MERCK- 7
Reply Dated September 16, 2003

This listing of claims will replace all prior versions, and listings, of claims in the application.

Listing of Claims:

1. (Currently Amended) A method of screening a substance for usefulness in the treatment of a lipid metabolism dysfunction comprising contacting said substance with a ROR α receptor, or ~~a response element~~ the response element of ROR located at position -198 to +24 of the apo C-III promoter involved in the regulation of the apo C-III gene, and measuring the level of apo C-III gene expression.

2. (cancelled)

3. (Currently Amended) A method of screening a substance for usefulness in the treatment of a lipid metabolism dysfunction, comprising contacting said substance with (a) a ROR α receptor involved in the regulation of the expression of the apo C-III gene, (b) ~~a response element of a ROR α receptor~~ the response element of ROR located at position -198 to +24 of the apo C-III promoter, or (c) a nuclear factor which functionally couples ROR α to a RNA polymerase complex, and then measuring:

i) the binding of said substance to the ROR α receptor or the binding of the complex formed by said substance and the ROR α receptor to ~~its~~ the response element or to a nuclear factor which couples ROR α to a RNA polymerase complex;

or

ii) the modulation of the transcriptional activity of a gene placed under the control of a promoter comprising said response element.

4. (Currently Amended) The method of screening according to claim 3, comprising:

- a) transfecting a cellular host with a DNA fragment encoding an ROR α receptor;
- b) cotransfecting the host in a) with a construct comprising ~~a response element of said ROR α receptor~~ the response element and at least one reporter gene; and
- c) measuring the expression of the reporter gene in the presence of the test substance.

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5. (Currently Amended) The method of screening according to claim 3, comprising:

- a) creating a plasmid which comprises several copies of a the response element recognized by ROR α cloned upstream of a strong heterologous promoter which controls the expression of a reporter gene;
- b) transfecting the construct of a) into host cells which express ROR α naturally or artificially;
- c) incubating the host cells of b) in the presence of the test substance; and
- d) measuring the activity of the reporter gene.

6. (Currently Amended) The method of screening according to claim 3, comprising:

- a) creating a plasmid which comprises several copies of a the response element recognized by ROR α cloned upstream of a promoter which controls the expression of a selectable gene;
- b) transfecting the construct of a) into a cellular host;
- c) cotransfecting the host of b) with the aid of a vector expressing ROR α ;
- d) incubating the host of c) in the presence of the test substance; and
- e) measuring the cellular survival of said cellular host in the presence of a toxic prodrug.

7. (Previously Presented) The method of screening according to claim 3, comprising:

- a) creating a plasmid which comprises several copies of a response element recognized by a yeast nuclear factor Gal4 cloned upstream of a strong promoter which controls the activity of a reporter gene;
- b) creating a plasmid from a chimera which comprises a DNA binding domain of Gal4 and a DEF domain of ROR α which are the ROR α domains to which the ligands bind;
- c) cotransfecting the plasmids in a) or b) into a cellular host;

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- d) incubating the host of c) in the presence of a test substance, and
- e) measuring the activity of said reporter gene.

8 (Currently Amended) The method of screening according to claim 3, comprising:

- a) transforming the cellular host with a construct carrying a gene encoding a ROR α receptor or a the response element of a ROR α receptor, and;
- b) assaying said cellular host or an extract thereof for the competitive displacement in the binding of labeled and unlabeled ligand to said ROR α receptor

9. (Currently Amended) The method of screening according to claim 4, wherein the construct carrying the gene encoding a ROR α receptor or a the response element of the ROR α receptor also comprises a reporter gene.

10. (Previously Presented) The method of screening according to claim 9, wherein the reporter gene is chosen from chloramphenicol acetyltransferase, the gene for luciferase from firefly or from Renilla, the gene for secreted alkaline phosphatase, the gene for beta-galactosidase or the gene for apo C-III.

11. (Previously Presented) The method of screening according to claim 4, wherein the cellular host is chosen from mammalian cells, bacteria, yeasts, or insect cells.

12. (Previously Presented) The method of screening according to claim 3, wherein the effect of said substance on the expression of said apo C-III gene is determined using transfection or analysis of mRNAs *in vitro* or on models *in vitro* or *in vivo*.

13. (cancelled)

14 (Previously Presented) A method for preparing a pharmaceutical composition or a medicament useful in treating or preventing atherosclerosis in humans or animals comprising selecting a substance screened according to claim 3.

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15. (Previously Presented) A method for treating or preventing atherosclerosis in humans or animals comprising modulating the expression of apo C-III using a medicament or a pharmaceutical composition comprising a substance selected according to claim 3.

16. (Currently Amended) A method for treating or preventing atherosclerosis in humans or animals comprising administering a medicament or a pharmaceutical composition comprising a substance which binds to a ROR α receptor, or ~~the~~ the response element of ROR located at position -198 to +24 of the apo C-III promoter involved in the regulation of the apo C-III gene.

17. (Previously Presented) The method according to claim 3, wherein the substance has antiatherosclerotic properties.

18. (Currently Amended) A method of screening according to claim 8, wherein the construct carrying a gene encoding the ROR receptor or a the response element of the ROR receptor also comprises a reporter gene

19. (Previously Presented) The method according to claim 1, wherein the lipid metabolism dysfunction is atherosclerosis

20. (Previously Presented) The method according to claim 2, wherein the lipid metabolism dysfunction is atherosclerosis.

21. (Previously Presented) The method of screening according to claim 4, wherein the lipid metabolism dysfunction is atherosclerosis.

22. (Currently Amended) A method of measuring the expression of the apo C-III gene, comprising contacting a substance with a ROR α receptor or a response element of the ROR α receptor located at position -198 to +24 of the apo C-III promoter ~~involved in the~~

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~~regulation of the expression of the apo C III gene or a response element of the ROR α receptor~~
or a nuclear factor which couples ROR α to a RNA polymerase complex, and then measuring:

i) the binding of said substance to the ROR α receptor or the binding of the complex formed by the said substance and the ROR α receptor to ~~its~~ the response element or to a nuclear factor which couples ROR α to a RNA polymerase complex;

or

ii) the modulation of the transcriptional activity of a gene placed under the control of a promoter comprising said response element.